

CASE REPORT

Spindle cell carcinoma of maxilla: Histomorphological and immunohistochemical analysis of a case

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ABSTRACT

The intriguing array of spindle cell lesions occurring, especially in the head and neck region, poses a critical diagnostic challenge not only to the histopathologist but also ultimately to the clinicians for planning an appropriate treatment protocol. Overlapping spectrum of clinico-radiographic and microscopic features further compounds this problem. In such situations, the aid of ancillary techniques like immunohistochemistry (IHC) is sought to clinch the diagnosis. But is the diagnosis based on IHC most decisive? Probably the answer lies in the Pandora's Box. This paper analyzed the potential doubts, apprehensions and the reliability that is singularly based on the morphological spindle appearance of an abnormal cell that has deviated from the usual clinical and microscopic presentation and thus posed a diagnostic dilemma warranting more questions than the answers. We review the etiopathogenesis of this entity and its differential diagnosis from few other spindle cell lesions of head and neck with special reference to use of immunohistochemical markers, with a case study.

Key words: Immunohistochemistry, spindle cell lesion, spindle cell carcinoma, sarcomatoid carcinoma

INTRODUCTION

Spindle cell lesions of head and neck include a diverse group of clinically and biologically heterogeneous lesions ranging from benign-reactive entities to malignancies.^[1] In this array, spindle cell carcinoma (SpCC) stands out as a rare malignant biphasic tumor comprising both epithelial and mesenchymal components, which is of presumed epithelial origin.^[2,3] The WHO classification has also placed this entity under malignant epithelial tumors of squamous cell carcinoma (SCC). The diagnostic criteria state that the presence of malignant spindle cells in addition to demonstration of invasive or *in situ* SCC or any evidence of epithelial differentiation of spindle cells are required to reveal SpCC.^[4] However, about one-third of the cases are monophasic, making diagnosis difficult.^[5] We report one such unusual case that occurred in the maxilla of a 40-year old patient and depicted exclusively spindle cell morphology. Exclusion of lesions like pleomorphic

sarcoma (PS), fibrosarcoma, rhabdomyosarcoma (RMS) and angiosarcoma (AS) by IHC was mandatory. The histogenesis of spindle cells in SpCC and the various differential diagnoses were reviewed.

CASE REPORT

A 40-year male patient reported to SCB Dental College, Cuttack, with a complaint of swelling in the anterior part of mouth. History revealed a rapidly growing mass in the anterior palatal gingiva with duration of 3 months. Histopathological study done elsewhere had diagnosed it as a pyogenic granuloma. Patient had habit of chewing tobacco since 10 years. Intra-oral examination revealed an exophytic, polypoidal pinkish red mass in the maxillary anterior gingiva measuring about 6 × 3.5 × 3.5 cm with an ulcerated surface [Figure 1]. Such aggressive clinical features along with history of rapid growth prompted us to review the previous histopathology slide that displayed foci of poorly differentiated polygonal squamous epithelial cells with abundant cytoplasm and round, vesicular nuclei, spindle cells, few bizarre cells and increased number of mitotic figures in the section [Figure 2]. There were areas in the section that mimicked granulation tissue [Figure 3]. Based on these features, a poorly differentiated carcinoma was diagnosed, although the possibility of a SpCC was kept in mind. There was no history of radiotherapy. Orthopantomogram showed presence

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of a radiolucent lesion in anterior maxilla [Figure 4]. Following baseline investigations partial maxillectomy was performed along with selective lymph node neck dissection involving level I and II. Grossing showed a multilobulated mass of dimension $3.8 \times 3.5 \times 3.5$ cm with partly resorbed alveolar and palatal bone. Microscopically, sections from different areas of the lesion revealed a highly cellular tumor with invading sheets of spindle cells with oval or round nuclei with vesicular chromatin, arranged in a fascicular and storiform pattern below a normal appearing stratified squamous epithelium. There was cellular pleomorphism, atypical and increased mitotic figures, giant cells, bizarre cells and few mixed inflammatory cells in a fibrous connective tissue stroma of increased vascularity [Figure 5]. However, there was no evidence of invasive island of epithelial cells or dysplastic epithelium, even in serial sections. The tumor was provisionally diagnosed as a spindle cell sarcoma. The spindle cell morphology and varied morphological presentation raised wide-ranging possibilities in diagnosis starting from PS, AS to RMS [Figures 6-8], respectively. Due to confusion and disparity over the diagnosis, immunohistochemistry (IHC) was done with markers pancytokeratin (Dako, AE1/AE3 clone),

epithelial membrane antigen (EMA, Dako, E29 clone), CD 10, vimentin, smooth muscle actin (SMA), S-100, HMB-45, CD 68, desmin (Biogenex, V9 and 33 clones, respectively) and CD34 (Dako, QBEnd10 clone). The spindle cells showed diffuse and intense cytoplasmic positivity with both AE1/AE3 and vimentin [Figures 9 and 10]. They showed negative staining for the other markers. Thus, tumor was diagnosed as SpCC. The nodes were free of any metastasis. The patient has remained on a 1-year uneventful follow-up since then without any recurrence.

DISCUSSION

The accurate diagnosis of spindle cell lesions of head and neck has always remained an enigma for the histopathologist. These lesions invariably occur in the skin, soft tissue of scalp, orbit, neck and along the upper aerodigestive tract.^[1-3] Spindle cell carcinoma is most predominant among them, occurring commonly in the larynx, hypopharynx and uncommonly in the oral cavity with less than 1% involving the lips, tongue, mandibular alveolar ridge and very few in maxilla.^[6-8] It usually occurs in the 6th-7th decades of life. The predisposing factors for SpCC include smoking, alcohol consumption and previous irradiation of head



Figure 1: Clinical image shows polypoidal growth in anterior alveolus

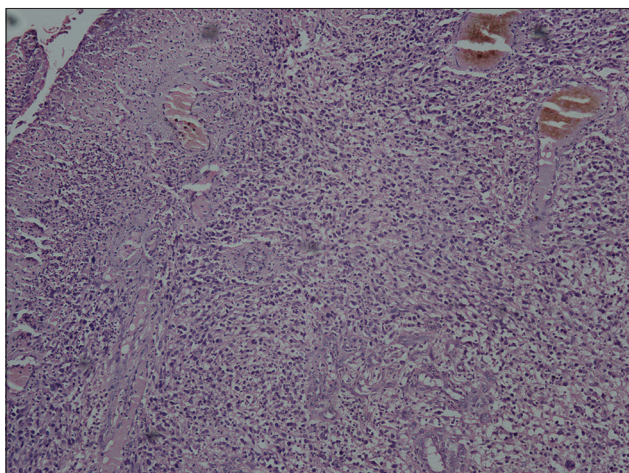


Figure 3: Photomicrograph shows spindle cells in loose stroma mimicking granulation tissue (H&E stain, x100)

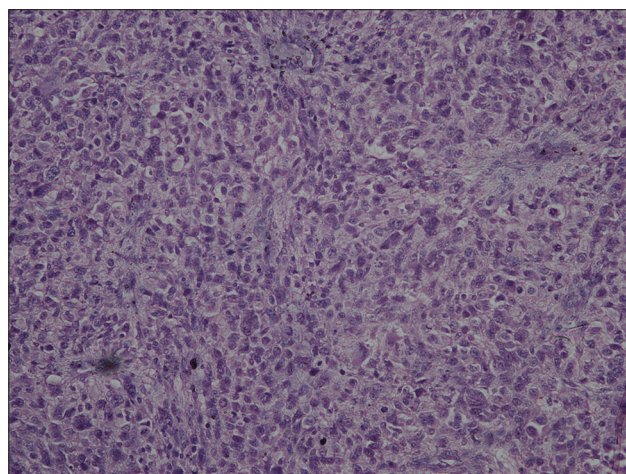


Figure 2: Photomicrograph shows poorly differentiated squamous cells with abundant cytoplasm and enlarged nuclei with vesicular chromatin (H&E stain, x200)



Figure 4: Orthopantomogram shows radiolucent lesion in anterior maxilla

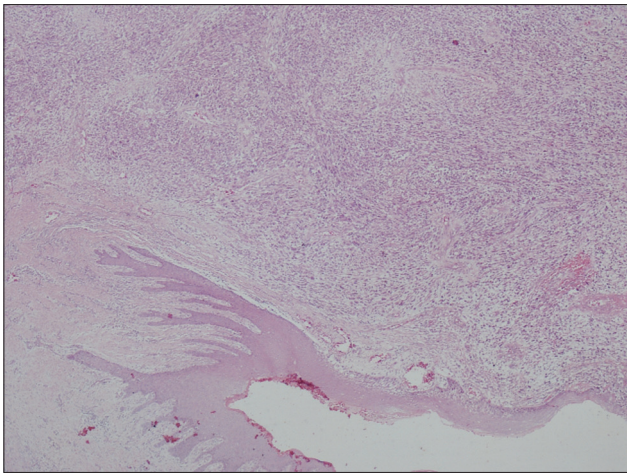


Figure 5: Photomicrograph shows proliferating sheets of spindle cells below a normal appearing stratified squamous epithelium (H&E stain, x40)

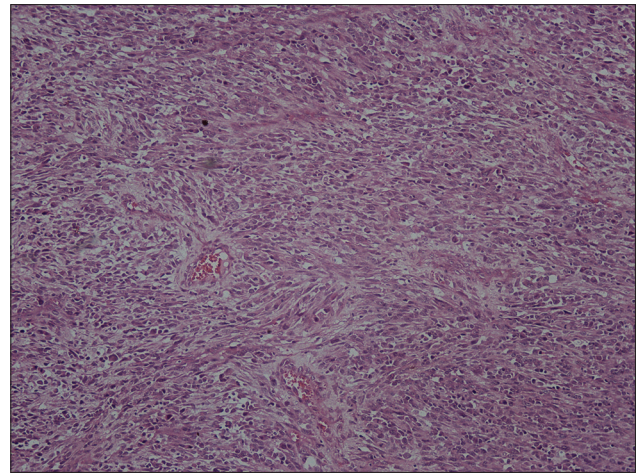


Figure 6: Photomicrograph shows pleomorphic spindle cells in storiform pattern with giant cells, resembling pleomorphic sarcoma (H&E stain, x100)

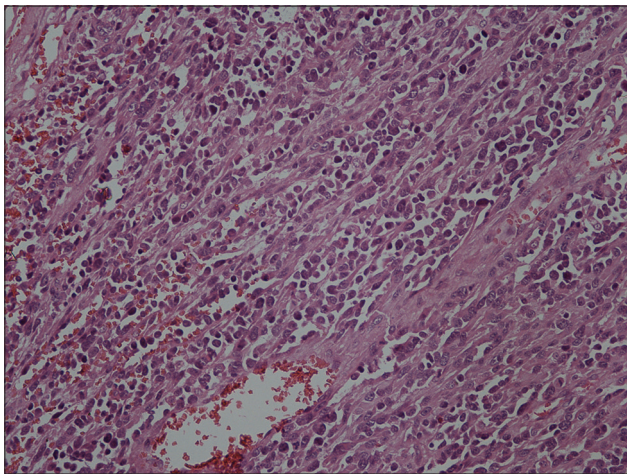


Figure 7: Photomicrograph shows atypical plump spindle cells with gaping vascular channels, akin to an AS (H&E stain, x200)

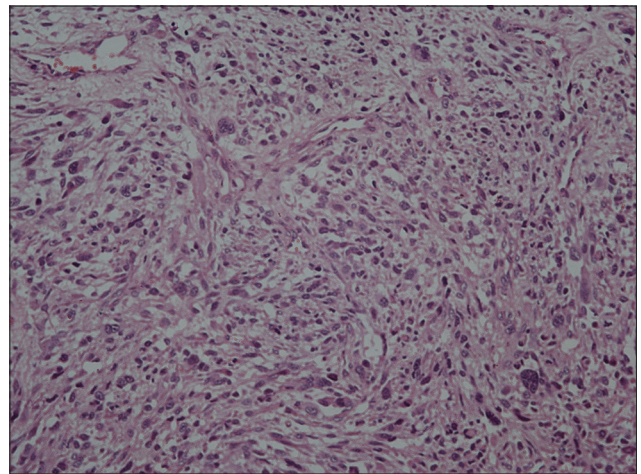


Figure 8: Photomicrograph shows pleomorphic and anaplastic spindle cells resembling pleomorphic RMS (H&E stain, x400)

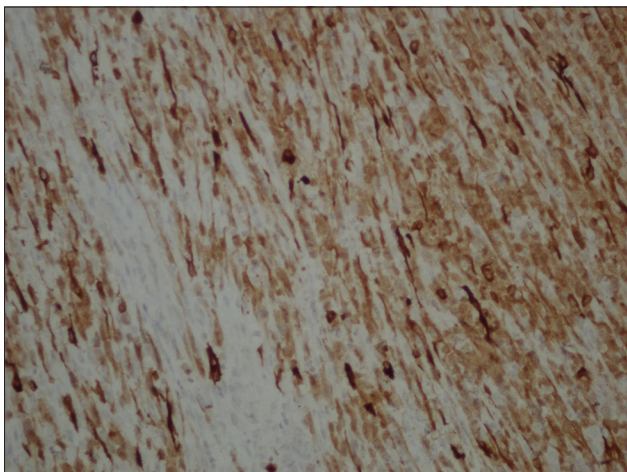


Figure 9: Photomicrograph showing diffuse and moderately intense positivity of spindle cells for pan cytokeratin (IHC stain, x400)

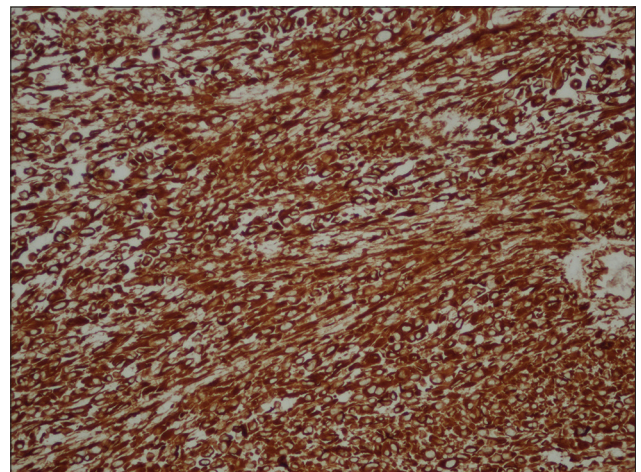


Figure 10: Photomicrograph showing intense cytoplasmic positivity for vimentin in the spindle cells (IHC stain, x100)

and neck.^[9] According to Lewis *et al.*, only 18% of SpCC in aerodigestive tract received radiotherapy.^[10] In a series of 103 similar oral cases, none of the patients had the history of radiation. The author suggested that this could be due to preferential surgery done in this locale instead of adjuvant radiotherapy.^[9] Spindle cell carcinoma mostly manifests as a rapidly growing exophytic, polypoidal mass or non-healing ulcer with symptoms of pain and swelling.^[2,3] Many consider it as an unusual form of poorly differentiated SCC with aggressive behavior.^[4,5] This case was unique by way of its occurrence at a younger age, in the maxilla and without prior history of radiotherapy.

The term SpCC was coined by Shervin *et al.*^[4] Despite immunohistochemical, ultrastructural and genetic studies, the histogenesis of SpCC remains controversial.^[10-12] The terminologies also reflect the varying interpretation of the spindle cell component. One of the theories suggests that the spindle cells and epithelial cells arise simultaneously from separate stem cells. Proponents of this theory argued that there is independent metastasis of the sarcomatous element and difference in immunohistochemical staining pattern between the epithelial and spindle cells.^[11] But this concept of a collision tumor or carcinosarcoma seemed rather unlikely as areas of transition exist between the two cell types.^[4] The term pseudosarcoma arose from the theory that the spindle component was a benign stromal proliferation to the SCC, but this was again doubtful as the spindle cells were found to be non-diploid suggesting their neoplastic nature.^[2,4] The monoclonal origin of SpCC and dedifferentiation theory of epithelial cells to spindle cells was supported by immunohistochemical studies where both the epithelial and spindle cells show positivity for cytokeratin and EMA.^[4,6,11] Double labeling indicated cytokeratin and vimentin positivity in individual spindle cells thus illustrating the versatility of the intermediate filament.^[12,13] Ultrastructural studies too have ascertained presence of desmosomes and tonofilaments, thus justifying the term sarcomatoid carcinoma.^[14] The basic defect is reported to be a dysfunctional cadherin-catenin complex resulting in alteration of the keratin filament network that shifts the morphology from squamoid to more spindled form. In addition, it is suggested that there is functional loss of genes that control epithelial differentiation and conversion to spindle morphology is a recessive entry.^[13,14]

In spite of debatable histogenesis, it is agreed that SpCC has both characteristic malignant epithelial and spindle cells, the latter appearing bland and regular or with marked pleomorphism, in a variety of architectural patterns including storiform, fascicular, or more definable sarcomatous differentiation.^[9,10] Multinucleated giant cells (MNGC) and numerous mitotic figures are also present.^[15] The squamous component appears in the form of either focal dysplasia, carcinoma *in situ* or frank SCC between the spindle cells and thus aids in diagnosis. Direct transition between the two cell types may be seen.^[5,6] Thompson *et al.* in their study found squamoid differentiation in 79.6% of SpCC cases.^[6] Other studies show that the squamous component can be found in

60-90% cases only.^[11] Our case showed sheet like proliferation of pleomorphic spindle cells without any obvious squamoid component. The lone presence of spindle cells might mislead the pathologist toward the diagnosis of other spindle cell lesions.^[1,2,6] An abnormal cell can take on a number of bizarre morphologies once there is loss of cellular control in them. Should a morphological feature like spindling of an abnormal cell be relied upon to term a tumor as SpCC? Is the mere presence of an epithelial-like or spindle-like morphology of an abnormal cell enough to designate a tumor as a carcinoma or sarcoma? Should we not go beyond these ambiguous histomorphological boundaries and look for other specific innate and qualifying characteristics like product of the tumor cells or ultrastructural elements that would be precisely diagnostic for lesions like the so called SpCC? In such a scenario, IHC detection of cytokeratin and vimentin is valuable, both of which are expressed in SpCC and may be considered diagnostic, especially in those cases where clear epithelial component is absent.^[1,6,10] It has been seen that even pancytokeratin positivity in spindle cells occurs in 26-62% cases.^[6,10,13,16] Therefore, reasonable queries may pertain for those minorities of cases where there is no routine light microscopic or immunohistochemical evidence of epithelial differentiation, toward diagnosis.^[1]

Vimentin has been regarded as the intermediate filament for mesenchymal cells, whereas keratin as the same for epithelial cells. However, now it is known that many epithelial cells in solid neoplasms like renal, ovarian and thyroid adenocarcinoma co-express vimentin and keratin.^[17-19] This co-expression of the markers is quite widespread and vimentin is of little importance in differentiating epithelial from mesenchymal neoplasms.^[17,18] It has also been seen that mesenchymal cells considered keratin-negative and some sarcomas can express cytokeratins.^[20] Thus, the utility of employing these markers in diagnosis is substantially reduced and inconclusive. Kramer has reviewed the various hypotheses behind the bimorphic differentiation of epithelial and mesenchymal parts in a single neoplasm and suggests that in light of these extraordinary IHC findings, the most attractive hypothesis to explain biphenotypic tumors is that they arise from uncommitted multipotential stem cells that differentiate in a non-random fashion where even primitive mesenchymal cells can acquire epithelial morphology and express cytokeratin and show ultrastructural evidence of epithelial differentiation.^[17,21] Therefore, it is time that we may transcend the morphology-based diagnosis and move on to genetic and molecular methods where meteoric clarity of evidence may surface to aid in the diagnosis.^[6,10] However, for routine cases these methods may not be cost-effective and are time consuming. In such a context, IHC may be decisive in most cases.^[1,6,10]

Due to the morphological diversity seen in monophasic spindled SpCC, there are a few common differentials that merit discussion. Spindle cell carcinoma may closely mimic

exuberant granulation tissue clinically and show areas with loose stroma, abundant small vessels with plump endothelial cell, fibroblasts and mixed inflammatory cells.^[1] Granulation tissue may even occur in cancer patients following radiotherapy. However, the short duration, small size, absence of cytologic atypia, few mitotic figures, no atypical mitosis and cytokeratin negativity help rule out SpCC.^[1] Another low-grade tumor that presents as an exophytic, ulcerated mass with submucosal proliferation of spindle cells in fascicles, increased cellularity, plump cells, highly vascular stroma and inflammatory cells and is positive for vimentin and occasionally cytokeratin is the inflammatory myofibroblastic tumor. Occurrence in younger age group, absence of atypia or atypical mitosis, spider-like cytoplasmic extensions and relative rarity help in differentiating it from SpCC.^[6]

Spindle cell carcinoma may be misinterpreted as fibrosarcoma due to the proliferation of spindle cells in well-organized fascicles and frequent mitotic activity, but the latter occur as slow-growing painless masses, lack the large and open nuclei with retained nucleolus of SpCC and much atypia, pleomorphism, or presence of bizarre giant cells and are negative for cytokeratin markers although positive for vimentin.^[15] When spindle cells in SpCC show a storiform arrangement, pleomorphism, giant cells, inflammatory cells, it may resemble undifferentiated high-grade pleomorphic sarcoma, which is however a rare sarcoma usually seen in older age and can be ruled out by its slow expansion, presence of numerous histiocytes, myxoid stroma, minimal atypia, foci of osteoid or cartilage metaplasia and negativity for cytokeratin and positivity for vimentin and CD68.^[8] Spindle cell RMS may

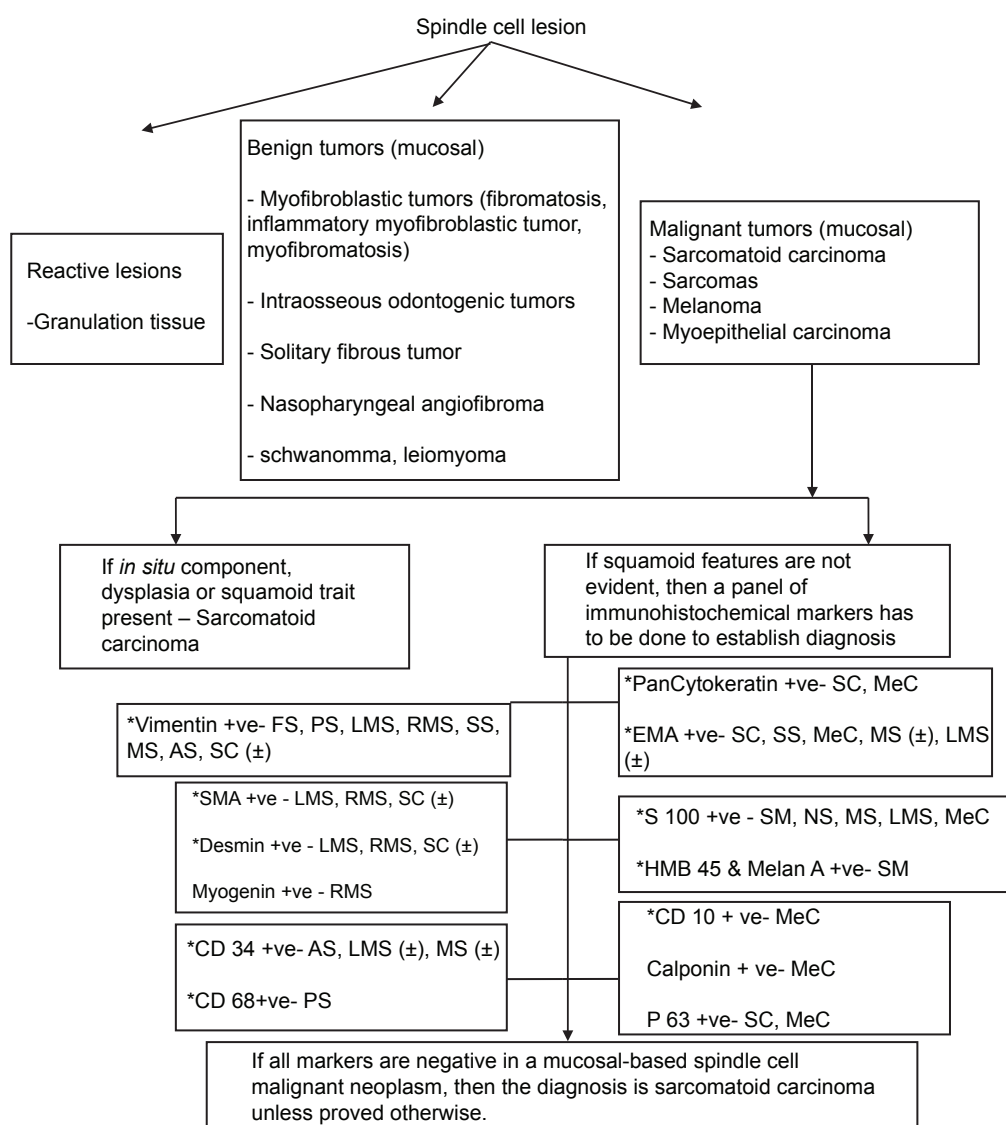


Figure 11: Diagnostic algorithm of mucosal spindle cell lesion based on morphology and immunohistochemistry

Footnote: SC: Sarcomatoid carcinoma, FS: Fibrosarcoma, PS: Pleomorphic sarcoma, LMS: Leiomyosarcoma, RMS: Rhabdomyosarcoma, AS: Angiosarcoma, SS: Synovial sarcoma, MS: Malignant schwannoma, NS: Neurogenic sarcoma, SM: Spindle cell melanoma, MeC: Myoepithelial carcinoma. SMA: Smooth Muscle Actin, EMA: Epithelial Membrane Antigen. (+) positive, (±) may be positive or negative. (*) The markers which were applicable and used in present case

comprise anaplastic spindle cells with bizarre configuration, MNGC, tadpole cells, frequent mitotic figures all of which may overlap with a monophasic SpCC. However, the relative rarity of spindle cell RMS in oral cavity, presence of striated cells, positive immunostaining with desmin, muscle-specific actin and myoglobin or ultrastructural demonstration of skeletal muscle differentiation may be diagnostic.^[15] The presence of spindle cells in a background of increased vascularity with distinct endothelium-lined vascular channels in an SpCC may be misdiagnosed as AS. However, the latter occur in older age, show tendency for anastomosis of vascular channels and proliferation of endothelial cell islands into vascular lumina. Besides they show positive immunostaining with CD34, CD31 and are negative for cytokeratin.^[15] The spindle cell morphology of leiomyosarcoma (LMS) may mimic an SpCC with presence of increased mitosis, hyperchromatic nuclei but rare occurrence of mucosal LMS, fascicular arrangement of spindle cells with abundant eosinophilic cytoplasm, blunt ended and palisaded nuclei discern it from an SpCC. Also LMS shows strong positivity for SMA, muscle-specific actin and desmin, which is absent in SpCC. Recently P63 has been indicated as a useful marker in diagnosis of SpCC.^[16] Although other spindle cell tumors like myoepithelial carcinoma, spindle cell melanoma, malignant schwannoma, synovial sarcoma subsist, they are comparatively rare. However, they need to be ruled out before diagnosing sarcomatoid carcinoma; therefore, an algorithm for diagnosing mucosal spindle cell lesions has been provided [Figure 11].

CONCLUSION

With increase in treatment including radiotherapy cases, SpCC would be frequently encountered in the clinical setting. Potentially aggressive with tendency to recur and metastasize, when diagnosed it has to be treated like an SCC in the same stage. Although it has an unpredictable biological behavior, tumors that are deeply invasive tend to have a poor prognosis than early stage tumors. A keen eye on the histomorphology, attention to clinical detail and judicious use of immunostains would help locate this ambiguous entity in the spindle cell lesion jargon.

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